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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,434	11/26/2003	Pingyu Zhong	26050-709.501	8676

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,434	ZHONG ET AL.	
	Examiner	Art Unit	
	PARITHOSH K. TUNGATURTHI	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 13-49* is/are pending in the application.

4a) Of the above claim(s) *13-27 and 29-32* is/are withdrawn from consideration.

5)☒ Claim(s) *7-9,28 and 33-39* is/are allowed.

6)☒ Claim(s) *40 and 45-49* is/are rejected.

7)☒ Claim(s) *41-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/15/2008 has been entered.

2. Claims 1-6 and 10-12 have been cancelled.

3. Claims 7-9, 36-39 and 42-44 have been amended.

4. Claims 13-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

5. Claims 7-9, 28, 33-49 are pending and under examination.

6. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Objections Withdrawn

7. The objection of claims 7-9, 36-39 and 42-44 is withdrawn in view of amendments to the claims.

Rejections Maintained

8. The rejection of claims 40 and 45-49 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibodies and antigen-binding fragments thereof comprising all six CDRs, three from the VH domain and three from the VL domain, does not reasonably provide enablement for anti-VEGF antibodies that do not consist of all six CDRs (as in claims 40 and 45-47) or just a VH domain or just a VL domain (as in claims 48 and 49). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The applicants argue that the methods for producing antibodies that bind a specific antigen by using a specific VL or VH and screening the library of the complementary variable domains were known in the art at the time of filing, and further point to Example 2 of the Slide presentation entitled "Enablement Issues in the Examination of Antibodies".

The above arguments are carefully considered but are not found persuasive. Claims 40, 45-47 are drawn to a monoclonal antibody wherein only three CDRs are defined, and claims 48 and 49 are drawn to an antibody heavy chain variable domain and light chain variable domain, respectively. Thus, none of the claims comprise all the necessary elements required for the antigen-binding property of an antibody. As stated in the previous office action mailed 10/15/2007, it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the

association of the complete heavy and light chain variable regions of a given antibody, each of which consists of four framework regions and three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Further, the applicant is pointed to Example 1 of the slide presentation (Exhibit 1 submitted by the applicant on 11/15/2008), wherein it is stated that the prior art for humanization supports obtaining successful antigen binding by transferring all the 6 CDRs from a donor framework to an acceptor framework. Thus, it is clear that all six CDRs are required for the antigen-binding activity of an antibody.

It is noted that in light of the prior art disclosing methods of obtaining antibodies that bind an antigen by screening complementary variable domain libraries, the specification's disclosure of an antibody that binds a specific antigen comprising a defined VH or VL sequence would provide enough structure for one skilled in the art to practice the invention as stated in Example 2 of Exhibit 1. However, such is not comprehensible for humanized antibodies because of high degree of variability, i.e. to identify the humanized VH or VL when only humanized VL or VH is disclosed; one must not only identify the complementary CDRs, but also the framework residues which in fact are involved in maintaining the antigen-binding structure. Thus, identification of a

humanized VH or a VL when given a humanized VL or VH is not carried out in the same fashion as it is for human or mouse antibodies. The references cited by the applicant refer to identifying a complementary variable chain for a human (Portolano et al) and a mouse (Clackson et al) antibody but not humanized antibodies. Hence the references are not considered pertinent because the instant claims are drawn to humanized antibodies.

Further, the applicant is reminded that the specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing humanized antibodies comprising less than all six CDRs that bind VEGF or an antibody VH or VL. The specification provides no direction or guidance regarding how to produce the myriad of antibodies. The specification does not provide any method of identifying a humanized VH when only a humanized VL is disclosed, either by phage display or mutagenesis methodologies. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must bear a reasonable correlation with the scope of enablement. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, in view of the lack of the predictability of the art to which the invention pertains as evidenced by the references cited above, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed humanized antibodies that bind VEGF with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent

working examples providing evidence which is reasonably predictive that the claimed antibodies bind VEGF, commensurate in scope with the claimed invention.

Conclusion

9. Claims 7-9, 28 and 33-39 are found allowable.

Claims 41-44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
Ph: (571) 272-8789

/David J Blanchard/
Primary Examiner, Art Unit 1643